REMARKS

I. Restriction/Election Requirement.

A Restriction requirement was raised between claim groups I, II, and III. Applicant elected group II, claims 89-139, and identified the species of claim 116. Accordingly, claims 68-88 and 140-145 are cancelled without prejudice or disclaimer.

II. Rejection Under 35 USC § 103(a).

Claims 89-102, 116, and 123-139 were rejected as obvious over Lindsay et al. (US 3,950,517), Markussen (US 5,008,241), Muranishi (JP 1-254699) and Gammeltoft (1984) Phys. Rev. 6494):1321-1378. This rejection is respectfully traversed.

The invention as claimed. Claim 89 is drawn to an insulin derivative having the sequence of SEQ ID NO:2 wherein the amino acid at position A21 and B3 are any amino acid except Lys, Arg, and Cys, the amino acid at position B1 is Phe or is deleted, and the amino acid at position B30 is deleted

The Lindsay et al. patent. Lindsay et al describe methods for reducing the antigenicity of porcine and bovine insulin by acylating the free amino groups at B1 (Phe), A1 (Gly) and the -amino group of B29 Lys. Specifically, the B1 Phe is protected with an acyl group or other blocking group having up to 7 carbon atoms; and the -amino group of B29 Lys is protected with an acyl group or another group having up to 4 carbon groups.

Lindsay et al. do not suggest or disclose an insulin derivative in which position B1 is deleted, or deletion of the amino acid at position B30.

The Markussen et al. patent. Markussen et al. describe human insulin analogs in which the Asn at position A21 is any other amino acid, preferably Glu, Asp, Lys, Arg, His, Val, Gln, Ile, Phe, Tyr, Met, Gly, Ser, Thr, Ala, Leu, Trp, and hSer (col. 3, lines 15-19). One set of preferred A21 substitutes is Lys, Arg, and His (col. 3, lines 23-25) Markussen further teaches the addition of an ester or amide group to position B30 to eliminate the negative charge, or the addition of a basic amino acid at the B30 position.

Markussen et al. do not suggest or disclose an insulin derivative in which the

The Muranashi et al. reference. Muranashi et al. describe insulin derivatives in which a fatty acid having 7-21 carbon atoms is attached to the amino acid at B1 or B29.

Muranishi et al. do not disclose or suggest an insulin derivative having the amino acid at position B1 deleted or the amino acid at B30 deleted.

The Gammeltoft reference. The Gammeltoft reference is a review article on the insulin receptor. Gammeltoft describes radiolabelled insulin preparations used to investigate ligand-receptor interactions, including iodinated insulin molecules labeled at position B1 Phe. Neither monoiodination or diiodination at B1 were found to alter biological potency (page 1327, lines 8-9). Degradation of porcine insulin (des-Ala B30) and des-tripeptide B28-B30 have been shown to retain receptor binding activity, whereas des-octapeptide B23-B30 is devoid of activity (p. 1351, 4th paragraph).

Gammeltoft does not describe a human insulin derivative in which the amino acid at B1 is deleted, and where A21 and B3 are any amino acid except Lys, Arg, and Cys which also has the amino acid at B30 deleted. Moreover, the cited prior art references, alone or in combination, fail to provide instructions for how one of skill in the art would select the instant insulin derivative.

The Analysis under § 103(a). Applicants respectfully submit that the Examiner has failed to establish a *prima facie* case of obviousness because none of the references, either alone or in combination, describe or suggest the claimed invention. The motivation to select through and modify the prior art must flow from some teaching in the art that suggests the desirability to make the necessary modifications to arrive at the instant invention. In re Napier, 55 F.3d 610, 613, 34 USPQ2d 1782, 1784 (Fed. Cir. 1995). The Examiner appears to believe that the cited prior art would lead one of skill in the art to use Lindsay et al. or Muranishi et al.'s addition of a protective acyl group to B29 Lys while simultaneously avoiding Markussen et al.'s direction to replace A21 Asn with Lys or Arg, and the addition of an amide group to B30, in combination with a modification of Gammeltoft's description of des-Ala B30 or des-tripeptide B28-B30 to delete the amino acid at B30. Such a belief is clearly unsupportable - the combined references may disclose

the cited references disclose an insulin derivative having a protracted profile of action and which is soluble at physiological pH. Accordingly, in light of the above remarks, Applicants request that this rejection be withdrawn.

Conclusion

In view of the above, it is respectfully submitted that all claims are in condition for allowance. Early action to that end is respectfully requested. The Examiner is hereby invited to contact the undersigned by telephone if there are any questions concerning this amendment or application

Respectfully submitted,

Date: 6 July 2001

Valeta A. Gregg, Reg. No. 35,127
Novo Nordisk of North America, Inc.
405 Lexington Avenue, Suite 6400
New York, NY 10174-6401
(212) 867-0123